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(54) **METHOD FOR TREATING GLAUCOMA COMPRISING ADMINISTERING α-LIPOIC ACID**

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See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,145,871	A *	9/1992	Cavazza	514/546
5,288,735	A *	2/1994	Trager et al.	514/363
5,364,884	A *	11/1994	Varma et al.	514/551
2002/0102581	A1	8/2002	Hageman et al.	
2004/0104646	A1	6/2004	Kelly et al.	

FOREIGN PATENT DOCUMENTS

WO	WO02/20028	*	3/2002

OTHER PUBLICATIONS

Gutteridge, Clinical and Exp. Optometry, vol. 83, 161-172, 2000.*
Filina et al., Vestn. Oftalmol. 1995 as printed by the Examiner from [www.ncbi.nlm.gov/pubmed]. pubmed# 8604540 obtained on Apr. 16, 2009, p. 1-2.*
Filina et al English Trnaslation: An English translation of Felina et al. Vestn. Oflalmol. 1995 by USPTO-STIC (PTO-09-4740), pp. 1-11.*
Lipoic acid: Medical Subject Headings printed by the Examiner from [www.nlm.nih.gov/cgi/mesh/2009] on Apr. 16, 2009, pp. 1-3.*
Abler, et al., Commun. Mol. Path. & Pharm. 92:177-189 (1996).
Ambati, J., et al., Surv. Ophthalmol. 48:257-293 (2003).
Asrani and Zeimer, Br. J. Ophthalm. 79(8):776-780 (1995).
Asrani, et al., Inv. Ophthalm. Vis. Sci. 38(13):2702-2710 (1997).
Bengtsson, Br J Ophthalmol, vol. 73, pp. 483-487 (1989).
Bressler, et al., Sur. Ophthalm, 32:375-413 (1988).
Brown, M., Drug Discov. Today 8:474-475 (2003).
Burns and Duff, Neurochem Res. 28:979-986 (2003).
Caricasole, A., et al., Trends Pharmacol. Sci. 24:233-238 (2003).
Chabry, J., et al., J. Neurosci. 23:462-469 (2003).
Chang, B-D., et al., Proc. Nat. Acad. Sci., USA 97:4291-4296 (2000).
Ciulla, et al., Sur. Ophthalm. 43:134-146 (1988).
Curcio, et al., Inv. Ophthalm. Vis. Sci. 37:1236-1249 (1996).
Damiens et al., Oncogene, 20(29):3786-3797 (2001).
Eldar-Finkelman, H., Trends Mol. Med. 8:126-132 (2002).
Ermilov et al., Arkh Patol, "Senile amyloidosis of the eye as a manifestation of senile cerebral amyloidosis", 43-45 (Russian) (1993).
Fakforovich, et al., Nature 347:83-86 (1990).
Frankiewicz and Parsons, Neuropharmacol. 38:1253-1259 (1999).
Ge-Zhi, et al., Trans. Am. Ophthalm. Soc. 94:411-430 (1996).
Gragoudas, et al., Inv. Ophthalm, Vis. Sci. 38(4)S17 (1997).
Gupta-Bansal and Brunden, J. Neurochem. 70:292-298 (1998).
Hock, C., et al., Amyloid: J. Prot. Fold. Disord. 10:1-6 (2003).
Husain, et al., Ophthalm. 104(8):1242-1250 (1997).
Janus, C., et al., Nature 408:979-982 (2000).
Jen, LS., et al., Nature 392:140-141 (1998).
Jensen, LE and Whitehead, AS, Biochem. J. 334:489-503 (1998).
Johan, K., et al., Proc. Nat. Acad. Sci. USA 95:2558-2563 (1998).
Kane, M.D., et al., J. Neurochem. 72:1939-1949 (1999).
Kindy, M.D., et al., J. Alzheimer's Disease 1:155-167 (1999).
Koriyama, Y., et al., Eur. J. Pharmacol. 458:235-241 (2003).
Krasnov, Vestn Oftalmol, "Morphological features of senile and secondary amyloidosis of the iris and sclera in patients with glaucoma" abstract (Jan.-Mar. 1996).
Kumon, Y., et al., Scand. J. Immunol. 53:7-12 (2001).
Kumon, Y., et al., Amyloid 9:237-241 (2002).
Kumon, Y., et al., Scand. J. Immunol. 56:504-511 (2002).
Lambert, M.P., et al., Proc. Nat. Acad. Sci. USA 95:6448-6453 (1998).
Lanz, T.A., et al., J. Pharmacol. Expt. Ther. 305:864-871 (2003).
LaVail, et al., Proc. Nat. Acad. Sci. 89:11249-11253 (1992).
Leske, M.C., et al., American Journal of Epidemilogy, 118(2):166-191 (Aug. 1983).
Liang, J.S., et al., Neurosci. Lett. 225:73-76 (1997).
Lin, et al., Curr. Eye Res. 13(7):513-522 (1994).
Liu, Y., et al., J. Neurochem. 69:2285-2293 (1997).
Marks, N. and Berg, M.J., Neurochem. Res. 28:1049-1062 (2003).
Matsuoka, Y., et al., J. Neurosci. 23:29-33 (2003).
Miida, T., et al., Biochem. 38(51):16958-16962 (1999).
Morgan, D., et al., Nature 408:982-985 (2000).
Naash, et al., Inv. Ophthalm, Vis. Sci. 37:775-782 (1996).
Nakagami, Y. and Oda, T., Jpn. J. Pharmacol. 88:223-226 (2002).
Nakagami, Y., et al., Br. J. Pharmacol. 137:676-682 (2002).
Nakagami et al., Eur J P, 457:11-17 (2002).
Noell, et al., Invest. Ophthalm. Vis. Sci. 5:450-472 (1966).
O'Hara, R., et al., Arthritis Res. 2:142 (2000).
Pike, C.J., et al., J. Neurosci. 13:1676-1687 (1993).
Schenk, D., et al., Nature 400:173-177 (1999).
Schwartz et al., Ophthalmology, 89(4):394-401 (1982).
Sickenberg, et al., Inv. Ophthalm. Vis. Sci. 38(4):S92 (1997).

(Continued)

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(57) **ABSTRACT**

The present invention provides compositions and methods for treating glaucoma, ocular hypertension, and age-related macular degeneration. More specifically, the present invention describes the use of agents that down-regulate expression of tanis and/or $p21^{Waf1/Cip1/Sd1}$ genes to treat such disorders of the eye.

1 Claim, No Drawings

OTHER PUBLICATIONS

Strong, N. P., "How optometrists screen for glaucoma: A survey", Ophthal. Physiol. Opt., 12:3-7 (1992).
Taylor, et al., Arch. Ophthalm. 110:99-104 (1992).
Thomas, et al., Inv. Ophthalm. Vis. Sci. 39(4):S242 (1998).
Thorn, C.F., et al., J. Immunol. 169:399-406 (2002).
Uhlar, C.M., et al., Eur. J. Biochem. 265:501-523 (1999).
Urieli-Shoval, S., et al., J. Histochem. Cytochem. 46:1377-1384 (1998).
Vaughan, D. et al., In: General Ophthalmology, Appleton & Lange, Norwalk, Conn., pp. 213-230 (1992).
Walder, et al., Diabetes 51:1859-1866 (2002).
Xia, W., Drug News Perspect. 16:69-73 (2003).
Xiang et al., (2002) Neurobiol. Aging 23:327-334.
Yamada, et al., Scand. J. Immunol. 52:7-12 (2000).
Yamazaki, et al., Biochemical and Biophysical Res. Comm. 290:1114-1122 (2002).
Yankner et al., Science, 250:279-282 (1990).
Young, Sur. Ophthalm. 32:252-269 (1988).
Zhang, L., et al., Neurosci. Lett. 312:125-128 (2001).

* cited by examiner

METHOD FOR TREATING GLAUCOMA COMPRISING ADMINISTERING α-LIPOIC ACID

This application claims priority from the provisional application, U.S. Patent Application Ser. No. 60/530,436 filed Dec. 17, 2003.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to the field of diagnosis and treatment of glaucoma. More specifically, the invention provides methods and compositions for treating ocular hypertension, glaucoma and age-related macular degeneration (ARMD) and for identifying therapeutic agents to treat these blinding diseases.

2. Description of the Related Art

There are a number of ocular conditions that are caused by, or aggravated by, damage to the optic nerve head, degeneration of ocular tissues, and/or elevated intraocular pressure. For example, "glaucomas" are a group of debilitating eye diseases that are a leading cause of irreversible blindness in the United States and other developed nations. Primary Open Angle Glaucoma ("POAG") is the most common form of glaucoma. The disease is characterized by the degeneration of the trabecular meshwork, leading to obstruction of the normal ability of aqueous humor to leave the eye without closure of the space (e.g., the "angle") between the iris and cornea (Vaughan, D. et al., (1992)). A characteristic of such obstruction in this disease is an increased intraocular pressure ("IOP"), resulting in progressive visual loss and blindness if not treated appropriately and in a timely fashion. The disease is estimated to affect between 0.4% and 3.3% of all adults over 40 years old (Leske, M. C. et al. (1986); Bengtsson, B. (1989); Strong, N. P. (1992)). Moreover, the prevalence of the disease rises with age to over 6% of those 75 years or older (Strong, N. P., (1992)).

Glaucoma affects three separate tissues in the eye. The elevated IOP associated with POAG is due to morphological and biochemical changes in the trabecular meshwork (TM), a tissue located at the angle between the cornea and iris. Most of the nutritive aqueous humor exits the anterior segment of the eye through the TM. The progressive loss of TM cells and the build-up of extracellular debris in the TM of glaucomatous eyes leads to increased resistance to aqueous outflow, thereby raising IOP. Elevated IOP, as well as other factors such as ischemia, cause degenerative changes in the optic nerve head (ONH) leading to progressive "cupping" of the ONH and loss of retinal ganglion cells and axons. The detailed molecular mechanisms responsible for glaucomatous damage to the TM, ONH, and the retinal ganglion cells are unknown.

Twenty years ago, the interplay of ocular hypertension, ischemia and mechanical distortion of the optic nerve head were heavily debated as the major factors causing progression of visual field loss in glaucoma. Since then, other factors including excitotoxicity, nitric oxide, absence of vital neurotrophic factors, abnormal glial/neuronal interplay and genetics have been implicated in the degenerative disease process. The consideration of molecular genetics deserves some discussion insofar as it may ultimately define the mechanism of cell death, and provide for discrimination of the various forms of glaucoma. Within the past 8 years, over 15 different glaucoma genes have been mapped and 7 glaucoma genes identified. This includes six mapped genes (GLC1A-GLC1F) and two identified genes (MYOC and

OPTN) for primary open angle glaucoma, two mapped genes (GLC3A-GLC3B) and one identified gene for congenital glaucoma (CYP1B1), two mapped genes for pigmentary dispersion/pigmentary glaucoma, and a number of genes for developmental or syndromic forms of glaucoma (FOXC1, PITX2, LMX1B, PAX6).

Thus, each form of glaucoma may have a unique pathology and accordingly a different therapeutic approach to the management of the disease may be required. For example, a drug that effects the expression of enzymes that degrade the extracellular matrix of the optic nerve head would not likely prevent RGC death caused by excitotoxicity or neurotrophic factor deficit. In glaucoma, RGC death occurs by a process called apoptosis (programmed cell death). It has been speculated that different types of insults that can cause death may do so by converging on a few common pathways. Targeting downstream at a common pathway is a strategy that may broaden the utility of a drug and increase the probability that it may have utility in the management of different forms of the disease. However, drugs that effect multiple metabolic pathways are more likely to produce undesirable side-effects. With the advent of gene-based diagnostic kits to identify specific forms of glaucoma, selective neuroprotective agents can be tested with the aim of reducing the degree of variation about the measured response.

Glaucoma is currently diagnosed based on specific signs of the disease (characteristic optic nerve head changes and visual field loss). However, over half of the population with glaucoma are unaware they have this blinding disease and by the time they are diagnosed, they already have irreversibly lost approximately 30-50% of their retinal ganglion cells. Thus, improved methods for early diagnosis of glaucoma are needed.

Current glaucoma therapy is directed to lowering IOP, a major risk factor for the development and progression of glaucoma. However, none of the current IOP lowering therapies actually intervenes in the glaucomatous disease process responsible for elevated IOP and progressive damage to the anterior segment continues. This is one possible reason why most patients become "resistant" to conventional glaucoma therapies. Thus, what is needed is a therapeutic method for altering (by inhibiting or even reversing) the disease process.

Another blinding disease is age-related macular degeneration (ARMD) that affects the outer retina, retinal pigmented epithelial cells, Bruch's membrane, and the choroid. (Ambati et al. 2003). The hallmarks of this disease are diffuse and focal thickening of the Bruch's membrane due to deposition of lipoproteins (drusen) leading to retinal dysfunction culminating in retinal detachment and loss of vision. Other lipoproteins, such as Tanis gene receptor and SAA, may also be deposited at the Bruch's membrane to exacerbate the pathology and retinal dysfunction.

There are several reports suggesting that primary amyloidosis may be associated with glaucoma. For example, it was found that amyloid was deposited in various ocular tissues including the vitreous, retina, choroid, iris, lens, and trabecular meshwork in primary systemic amyloidosis patients (Schwartz et al. 1982). Ermilov et al. (1993) reported that in 478 eyes of 313 patients (aged 25 years to 90 years) with cataracts, glaucoma, and/or diabetes mellitus, 66 (14%) of the eyes contained amyloid-pseudoexfoliative amyloid (PEA) proteins. Krasnov et al. (1996) reported that 44.4% of 115 patients with open-angle glaucoma revealed extracellular depositions of amyloid proteins. Finally, amyloidosis was revealed in the sclera in 82% of the cases and in the iris in 70% of the cases. A number of clinical conditions, including Alzheimer's disease, exhibit abnormal amyloid deposits in

tissues associated with the disease. However, amyloids are molecularly heterogeneous and encoded by different amyloid genes. The previous reports are unclear regarding which amyloid(s) might be associated with glaucoma.

To date, more than 100 genes have been mapped or cloned that may be associated with retinal degeneration. The pathogenesis of retinal degenerative diseases such as age-related macular degeneration (ARMD) and retinitis pigmentosa (RP) is multifaceted and can be triggered by environmental factors in those who are genetically predisposed. One such environmental factor, light exposure, has been identified as a contributing factor to the progression of retinal degenerative disorders such as ARMD (Young 1988). Photo-oxidative stress leading to light damage to retinal cells has been shown to be a useful model for studying retinal degenerative diseases for the following reasons: damage is primarily to the photoreceptors and retinal pigment epithelium (RPE) of the outer retina (Noell et al. 1966; Bressler et al. 1988; Curcio et al. 1996); they share a common mechanism of cell death, apoptosis (Ge-Zhi, et al. 1996; Abler et al. 1996); light has been implicated as an environmental risk factor for progression of ARMD and RP (Taylor et al. 1992; Naash et al. 1996); and therapeutic interventions which inhibit photo-oxidative injury have also been shown to be effective in animal models of neurodegenerative retinal disease (LaVail et al. 1992; Fakforovich et al. 1990).

To date, there are no approved effective therapies for the treatment of ocular neovascular diseases which do not include the destruction of healthy viable tissue. There are certainly no therapies specifically directed at eliminating or inhibiting the deposition and accumulation of amyloid proteins, drusen or amyloid-like proteins including SAA on the Bruch's membrane in the retina as in ARMD. Such accumulation of amyloid and/or drusen and other lipoproteins including SAA causes retinal dysfunction by several mechanisms including disruption of retinal pigmented epithelial (RPE) cell function due to thickening of Bruch's membrane, and RPE detachment resulting in rapid loss of visual acuity followed by macular atrophy and retinal detachment (Ciulla et al. 1998). Additionally, the deposited drusen and/or amyloid proteins including SAA could exert direct neurotoxic effects on the RPE cells and neighboring cells in the retina akin to the well known toxic effects of such amyloid proteins and amyloid/lipid complexes observed in brain cell death as in Alzheimer's disease (Lambert et al. 1998; Liu and Schubert 1997; Pike et al. 1993; Nakagami et al. 2002) in retina (Jen et al. 1998). Although panretinal photocoagulation is the current medical practice for the treatment of diabetic retinopathy and ARMD and is effective in inhibiting retinal neovascularization, this procedure destroys healthy peripheral retinal tissue. This destruction of healthy tissue decreases the retinal metabolic demand and thereby reduces retinal ischemia driven neovascularization. Photodynamic therapy (PDT) is a procedure in which a photoactivatable dye is given systemically followed by laser activation of the dye in the eye at the site of new blood vessel formation (Asrani & Zeimer 1995; Asrani et al. 1997; Husain et al. 1997; Lin et al. 1994). The photoactivated drug generates free oxygen radicals which seal the newly formed blood vessels and thereby prevent or reduce their growth, at least temporarily. This procedure has been used in patients with the exudative form of macular degeneration and many patients show regression of their subretinal neovascular membranes. Unfortunately, it appears that the PDT-induced inhibition of retinal neovascularization is risky, expensive and provides transient and temporary relief lasting only 6-12 weeks (Gragoudas et al. 1997; Sickenberg et al. 1997; Thomas et al. 1998).

Thus, there is an urgent need for therapeutic methods for altering (by inhibiting or even reversing) the disease processes of glaucoma and ARMD.

SUMMARY OF THE INVENTION

The present invention overcomes these and other drawbacks of the prior art by providing methods to diagnose and compositions to treat ocular hypertension, glaucoma and ARMD. The present invention overcomes these and other drawbacks of the prior art by providing compositions and methods for treating ARMD by sequestering and/or degrading Tanis gene product protein (TGPP) and/or $p21^{Waf1/Cop1/Sdi1}$ gene product protein (p21GPP) in ocular tissues at the back of the eye, specifically at the Bruch's membrane, outer retina, macula and sub-retinal space. In addition, compositions and methods to prevent the generation of TGPP and/or p21GPP and/or to prevent the neurotoxic effects of such gene product proteins are provided to treat ARMD. In one aspect, the present invention provides a method for treating ARMD by administering to a patient in need thereof a therapeutically effective amount of a composition comprising an agent that sequesters TGPP or p21GPP in ocular tissue and/or an agent that degrades TGPP or p21GPP in ocular tissue. Such sequestration and/or degradation modulates the expression of the TGPP and p21GPP, such that the patient's condition is treated. In addition, agents that stop or reduce the initial activation of Tanis and $p21^{Waf1/Cop1/Sdi1}$ genes and/or prevent nerve cell death due to the presence of TGPP or p21GPP would also be useful to treat the patient's ARMD condition. In preferred embodiments, the agent will be a small molecular weight molecule, antibody, protein, peptide, peptidomimetic, or nucleic acid.

Preferably, the agents for use in the compositions and methods of the present invention will mainly be chosen from the following:

Compounds that may be useful for preventing the production of TGPP or p21GPP would include: γ-secretase inhibitors such as talsaclidine (Hock et al. 2003), Xanomeline, 3-(2-6-chloropyrazinyl)-1-azabicyclo(2.2.2)octane (L-689660), 1-benzyl-4-(1-(1 carbamoyl-2-phenylethylcarbamoyl-3-methylbutylcarbamoyl)-2-hydroxy-5-phenylpentyl)carbamic acid tert-butyl ester (L-685458), (4-(m-Chlorophenylcarbamoyloxy)-2-butynyl)trimethylammonium Chloride (McN-A-343), 5-propargyloxycarbonyl-1,4,5,6-tetrahydropyrimidine hydrochloride (CDD-0097), fenchylamine, Z-leu-leu-leu-CHO (MG132), Boc-PheΨPhe-Leu-Val-OMe (WPE-111-31C, where Ψ is the pseudopeptide bond containing the hydroxyethyl group), (MW-11-36C/26A), Boc-Val-Ile-NH—$CH(CH_3)$—C(=O)—$CH(F_2)$—C(=O)—NH-Val-Ile-OMe (MW-167), CM-265, lactacystin, DNPS1 and N—[N-(3,5-difluorophenacetyl)-L-alanyl]-S-phenylglycine t-butyl ester (DAFT) (Lanz et al. 2003). Other compounds of use may include the statin family, e.g. pravastatin, atorvastatin (see Burns and Duff 2003) and presenilinase inhibitors such as pepstatin A (Xia 2003) and talsaclidine (Hock et al. 2003).

Compounds that may be useful for promoting degradation of TGPP or p21GPP may include glycoaminoglycans and congo red (*J. Neurochem.* 70: 292-298 [1998]).

Compounds that may be useful for promoting sequestration or clearance of TGPP or p21GPP may include gelsolin and ganglioside GM1 (Matsuoka et al. 2003). In addition, antibodies raised against drusen, and/or amyloid proteins and/or against amyloid-like proteins would be useful for sequestration and clearance of the former detrimental pro-

teins as has been shown in the brain (Schenk et al. 1999; Janus et al. 2000; Morgan et al. 2000).

Compounds that may be useful for preventing or diminishing the neurotoxic effects of TGPP or p21GPP include RS-0466 (Nakagami et al. 2002c; Nakagami et al. 2002b), V-type ATPase inhibitors (bafilomycin and concanamycin; Kane et al. 1999), tachykinin peptides and their non-peptide analogs (Yankner et al. 1990), α-lipoic acid (Zhang et al. 2001), propentofylline (Koriyama et al. 2003), glycogen synthase kinase-3β (GSK-3β) inhibitors (Eldar-Finkelman 2002; Caricasole et al. 2003), memantine (Frankiewicz and Parsons 1999), mixed cyclin-dependent kinase-GSK3β inhibitors (Damiens et al. 2001), COX-2 inhibitors (Xiang et al. 2002) and propentofylline (Koriyama et al. 2003).

The present invention further provides a method of treating glaucoma by administering a composition containing a $p21^{Waf1/Cip/Sdi1}$ gene product protein (see below) inhibitor and/or inhibitors of CDK1, CDK2, CDK5 and CDK9, and inhibitors of cJAK and ASRK-1 including the following agents: olomoucine, roscovitine, purvalanol, kenpaullone, alsterpaullone, indirubins, flavopiridol, stauroporine and analogs and derivatives of the above compounds.

In one aspect, the present invention provides a method for treating glaucoma by administering to a patient in need thereof a therapeutically effective amount of a composition comprising an agent that interacts with a gene encoding a serum amyloid A (SAA) receptor (SEQ ID NO:12), wherein said interaction decreases the expression of SAA (SEQ ID NO:1).

In another aspect, the present invention provides a method for treating glaucoma by administering to a patient in need thereof a therapeutically effective amount of a composition comprising a Tanis antagonist.

In preferred aspects, the agent for use in the methods of the invention is a peroxisome proliferator-activated receptor α (PPARα) agonist, tachykinin peptide or non-peptide analogs thereof, or α-lipoic acid. More preferably, the agent is fenofibrate, Wy-14643, (4-chloro-6-(2,3-xylidino)-2-pyrimidinylthiol)-acetic acid), ciprofibrate, 2-bromohexadecanoic acid, bezafibrate and ciglitizone, bafilomycin or concanamycin.

In yet another aspect, the invention provides a method for treating glaucoma by administering to a patient in need thereof a therapeutically effective amount of a composition comprising a p21 antagonist.

The present invention further provides a pharmaceutical composition comprising a therapeutically effective amount of a Tanis antagonist and a pharmaceutical carrier.

DETAILED DESCRIPTION PREFERRED EMBODIMENTS

Glaucoma is a heterogeneous group of optic neuropathies that share certain clinical features. The loss of vision in glaucoma is due to the selective death of retinal ganglion cells in the neural retina that is clinically diagnosed by characteristic changes in the visual field, nerve fiber layer defects, and a progressive cupping of the ONH. One of the main risk factors for the development of glaucoma is the presence of ocular hypertension (elevated intraocular pressure, IOP). IOP also appears to be involved in the pathogenesis of normal tension glaucoma where patients have what is often considered to be normal IOP. The elevated IOP associated with glaucoma is due to elevated aqueous humor outflow resistance in the trabecular meshwork (TM), a small specialized tissue located in the iris-corneal angle of the ocular anterior chamber. Glaucomatous changes to the TM include a loss in TM cells and the deposition and accumulation of extracellular debris including proteinaceous plaque-like material. In addition, there are also changes that occur in the glaucomatous optic nerve head (ONH). In glaucomatous eyes, there are morphological and mobility changes in ONH glial cells. In response to elevated IOP and/or transient ischemic insults, there is a change in the composition of the ONH extracellular matrix and alterations in the glial cell and retinal ganglion cell axon morphologies.

It has been found that the expression of Serum Amyloid A (SAA) mRNA is significantly upregulated in glaucomatous TM tissues and cells. The differential expression seen has been verified using Affymetrix gene chips by real time quantitative polymerase chain reaction (QPCR). This is the first time SAA has been shown to be expressed in the TM (U.S. application Ser. No. 60/530,430).

Human SAA comprises a number of small, differentially expressed apolipoproteins encoded by genes localized on the short arm of chromosome 11. There are four isoforms of SAAs. SAA1 (SEQ ID NO:2), encoded by SEQ ID NO:1, and SAA2 (SEQ ID NO:4), encoded by SEQ ID NO:3, are known as acute phase reactants, like C-reactive protein, that is, they are dramatically upregulated by proinflammatory cytokines. The 5'UTR promoter regions of SAA1 and SAA2 genes are also provided (SEQ ID NO:12 and SEQ ID NO:13, respectively). SAA3 (SEQ ID NO:5) is a pseudogene and SAA4 (SEQ ID NO:6) is a low level endogenously expressed gene encoding endogenous SAA4 (SEQ ID NO:7). SAA2 has two isoforms, SAA2α (SEQ ID NO:9), encoded by SEQ ID NO:8, and SAA2β (SEQ ID NO:11), encoded by SEQ ID NO:10, which differ by only one amino acid. SAA1 and SAA2 proteins are 93.5% identical at the amino acid level (SEQ ID NO:2 and SEQ ID NO:4, respectively) and these genes are 96.7% identical at the nucleotide level (SEQ ID NO:1 and SEQ ID NO:3, respectively).

SAA functions as an apolipoprotein and is expressed in a number of tissues in addition to the liver (Miida et al. 1999). However, over-expression of SAA1 or SAA2 leads to the formation of linear fibrils in amyloid deposits, which can lead to pathogenesis and thus many types of diseases (Uhlar and Whitehead 1999; Liang et al. 1997). SAA plays an important role in infections, inflammation, and in the stimulation of tissue repair. SAA concentration may increase up to 1000-fold following inflammation, infection, necrosis, and decline rapidly following recovery. Thus, serum SAA concentration is considered to be a useful marker with which to monitor inflammatory disease activity. Hepatic biosynthesis of SAA is up-regulated by pro-inflammatory cytokines, leading to an acute phase response. Chronically elevated SAA concentrations are a prerequisite for the pathogenesis of secondary amyloidosis, a progressive and sometimes fatal disease characterized by the deposition in major organs of insoluble plaques composed principally of proteolytically cleaved SAA. This same process also may lead to atherosclerosis. There is a requirement for both positive and negative SAA control mechanisms to maintain homeostasis. These mechanisms permit the rapid induction of SAA expression to fulfill host-protective functions, but they also must ensure that SAA expression is rapidly returned to baseline levels to prevent amyloidosis. These mechanisms include modulation of promoter activity involving, for example, the inducer nuclear factor kB (NF-kB) and its inhibitor IkB, up-regulation of transcription factors of the nuclear factor for interleukin-6 (NF-IL6) family, and transcriptional repressors such as yin and yang 1 (YY1). Post-transcriptional modulation involving changes in mRNA stability and translation efficiency permit further up- and down-regulatory control of SAA protein synthesis to be achieved. In the later stages of the AP response,

SAA expression is effectively down-regulated via the increased production of cytokine antagonists such as the interleukin-1 receptor antagonist (IL-1Ra) and of soluble cytokine receptors, resulting in less signal transduction driven by pro-inflammatory cytokines (Jensen and Whitehead, 1998).

There are several reports suggesting that primary amyloidosis may be associated with glaucoma. For example, it was found that amyloid was deposited in various ocular tissues including the vitreous, retina, choroid, iris, lens, and TM in primary systemic amyloidosis patients (Schwartz et al. 1982). Ermilov et al. (1993) reported that in 478 eyes of 313 patients, aged 25 years to 90 years, with cataracts, glaucoma, and/or diabetes mellitus, 66 (14%) of the eyes contained amyloid-pseudoexfoliative amyloid (PEA). Krasnov et al. (1996) reported that 44.4% of 115 patients with open-angle glaucoma revealed extracellular depositions of amyloid. Amyloidosis was revealed in the sclera in 82% of the cases and in the iris in 70% of the cases. A number of clinical conditions, including Alzheimer's disease, exhibit aberrant amyloid tissue deposits associated with disease. However, amyloids are molecularly heterogeneous and encoded by different amyloid genes. The previous reports are unclear regarding which amyloid(s) are associated with glaucoma.

SAA gene expression is elevated significantly in glaucomatous TM tissues. Increased SAA may be involved in the generation of elevated IOP and damage to the optic nerve leading to vision loss in glaucoma patients.

The Tanis gene (SEQ ID NO:14) is a recently identified gene that encodes a membrane protein (SEQ ID NO:15) said to bind to SAA (Walder et al. 2002). It is believed that therapeutic intervention of the interaction between SAA and its putative receptor, encoded by the Tanis gene, may modulate SAA expression levels and/or receptor-mediated SAA signaling. Methods for the identification of agents that interfere with this interaction and their use for the treatment of ocular hypertension, glaucoma and ARMD are also provided herein.

It has also recently been discovered that a gene called $p21^{Waf1/Cip/Sdi1}$ (SEQ ID NO:16) activates SAA and activates the gene APP that produces amyloid protein which forms plaques in the brain that are hallmarks of Alzheimer's disease (Chang et al 2000; Kindy et al. 1999; Johan et al. 1997). In addition, $p21^{Waf1/Cip/Sdi1}$-induced gene expression results in over production of extracellular matrix (ECM) proteins including fibronectin-1, plasminogen activator inhibitor, tissue-type plasminogen activator, integrin β3 (Chang et al. 2000) which may be contributive factors in the glaucomatous situation. Likewise, $p21^{Waf1/Cip/Sdi1}$-induced connective tissue growth factor and galectin-3 (Chang et al. 2000) may also play significant roles in deposition of ECM proteins and other components of ECM in the anterior eye segment leading to ocular hypertension and glaucoma. Therefore, it is believed that inhibition of $p21^{Waf1/Cip/Sdi1}$ gene would be useful in the treatment of the pathophysiology of glaucoma. Interestingly, since $p21^{Waf1/Cip/Sdi1}$ gene expression results in natural inhibition of cyclin-dependent kinases (CDK) (Chang et al. 2000), and since $p21^{Waf1/Cip/Sdi1}$ was reported to bind c-Jun amino-terminal kinase (cJAK), apoptosis-signal-regulating kinase 1 (ASRK-1) and Gadd45 (Chang et al. 2000), it follows that inhibitors of these kinases would also act as $p21^{Waf1/Cip/Sdi1}$ antagonists. Accordingly, inhibitors of CDK1, 2, 5 and 9, and inhibitors of cJAK and ASRK-1 would be useful for treating ocular hypertension, glaucoma and ARMD. Agents which may modulate the interaction of SAA and its putative receptor and the TGPP or p21GPP include, but are not limited to, peroxisome proliferator-activated receptor α (PPARα) agonists, tachykinin peptides and their non-peptide analogs, and α-lipoic acid. PPARα agonists include arachidonic acid, linoleic acid, docosahexaenoic acid, eicosapentaenoic acid, 8(S)-HETE, (±)ibuprofin, indomethacin, leukotriene B_4, meclofenamate, prostaglandin A_1, prostaglandin A_2, prostaglandin D_1, prostaglandin D_2, prostaglandin J_2, 15-deoxy-Δ^{12}-prostaglandin J_2, WY 14643, ciglitizone, carbaprostacyclin and prostacyclin. Examples of preferred agents for use in the present invention include fenofibrate, WY 14643, (4-chloro-6-(2,3-xylidino)-2-pryrimidinylthiol)-acetic acid), ciprofibrate, 2-bromohexadecanoic acid, bezafibrate, ciglitizone, bafilomycin, and concanamycin.

In another aspect the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of a Tanis gene product protein inhibitor and/or Tani gene inhibitor or a $p21^{Waf1/Cip/Sdi1}$ gene inhibitor or $p21^{Waf1/Cip/Sdi1}$ gene product protein inhibitor and a pharmaceutical carrier.

The Compounds of this invention, can be incorporated into various types of ophthalmic formulations for delivery to the eye (e.g., topically, intracamerally, or via an implant). The Compounds are preferably incorporated into topical ophthalmic formulations for delivery to the eye. The Compounds may be combined with ophthalmologically acceptable preservatives, surfactants, viscosity enhancers, penetration enhancers, buffers, sodium chloride, and water to form an aqueous, sterile ophthalmic suspension or solution. Ophthalmic solution formulations may be prepared by dissolving a Compound in a physiologically acceptable isotonic aqueous buffer. Further, the ophthalmic solution may include an ophthalmologically acceptable surfactant to assist in dissolving the Compound. Furthermore, the ophthalmic solution may contain an agent to increase viscosity, such as, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, methylcellulose, polyvinylpyrrolidone, or the like, to improve the retention of the formulation in the conjunctival sac. Gelling agents can also be used, including, but not limited to, gellan and xanthan gum. In order to prepare sterile ophthalmic ointment formulations, the active ingredient is combined with a preservative in an appropriate vehicle, such as, mineral oil, liquid lanolin, or white petrolatum. Sterile ophthalmic gel formulations may be prepared by suspending the Compound in a hydrophilic base prepared from the combination of, for example, carbopol-974, or the like, according to the published formulations for analogous ophthalmic preparations; preservatives and tonicity agents can be incorporated.

The Compounds are preferably formulated as topical ophthalmic suspensions or solutions, with a pH of about 4 to 8. The establishment of a specific dosage regimen for each individual is left to the discretion of the clinicians. The Compounds will normally be contained in these formulations in an amount 0.01% to 5% by weight, but preferably in an amount of 0.05% to 2% and most preferably in an amount 0.1 to 1.0% by weight. The dosage form may be a solution, suspension microemulsion. Thus, for topical presentation 1 to 2 drops of these formulations would be delivered to the surface of the eye 1 to 4 times per day according to the discretion of a skilled clinician.

The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

Example 1

Formulation of Tanis Gene (TG) Inhibitor or TG Product Protein Inhibitor or p21$^{Waf1/Cip/Sdi1}$ Gene Inhibitor or Inhibitor of p21$^{Waf1/Cip/Sdi1}$ Gene Product Protein for Topical Ocular Application

1% suspension or solution of Tanis gene inhibitor (TGI) or inhibitor of Tanis gene product protein (TGPPI) or p21$^{Waf1/Cip/Sdi1}$ gene inhibitor (p21GI) or inhibitor of p21G product protein (p21GPPI) for topical ocular application:

Description	Conc.	Units	Purpose
TGI or TGPPI or p21GI or p21GPPI	1%	W/V%	active ingredient
hydroxypropyl methylcellulose (2910) (E4M), USP	0.5%	W/V %	viscosity modifier
dibasic sodium phosphate (anhydrous), usp	0.2%	W/V %	buffering agent
sodium chloride, usp	0.75%	W/V %	tonicity agent
disodium edta (edetate disodium), usp	0.01%	W/V %	chelating agent
polysorbate 80, nf	0.05%	W/V %	wetting agent
benzalkonium chloride, nf	0.01%	W/V %	preservative
sodium hydroxide, nf	q.s. pH	W/V %	pH adjust
hydrochloric acid, nf	q.s. pH	W/V %	pH adjust
purified water, usp	q.s. 100%	W/V %	vehicle

In similar other examples, TGI or TGPPI or p21GI or p21GPPI will be substituted by agents that sequester or degrade the above or agents that prevent the toxic effects of the above.

Methods to measure the potency or efficacy of agents that can inhibit the secretion of SAA from cultured cells involve the use of an enzyme-linked immunosorbant assay (ELISA) for human SAA as described by Yamada et al. (2000) and using human peripheral monocytes and monocytic leukaemic cell-line THP-1. In addition, methods to determine the potency and efficacy of agents to inhibit gene expression of p21$^{Waf1/Cip/Sdi1}$ can be studies using standard methods described by Chang et al. (2000).

All of the compositions and/or methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of this invention have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the compositions and/or methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the invention. More specifically, it will be apparent that certain agents which are both chemically and structurally related may be substituted for the agents described herein to achieve similar results. All such substitutions and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the invention as defined by the appended claims.

REFERENCES

The following references, and the bibliography cited within these, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

PUBLICATIONS

Abler et al., Res. Commun. Mol. Path. & Pharm. 92:177-189 (1996).

Ambati, J. et al., *Age-related macular degeneration: etiology, pathogenesis, and therapeuic strategies*. Surv. Ophthalmol. 48: 257-293 (2003).

Asrani et al., Inv. Ophthalm. Vis. Sci. 38(13):2702-2710 (1997).

Asrani and Zeimer, Br. J. Ophthalm. 79(8):776-780 (1995).

Bressler et al., Sur. Ophthalm. 32:375-413 (1988).

Brown, M., *Gene therapy success for Alzheimer's?* Drug Discov. Today 8:474-475 (2003).

Caricasole, A. et al., *The Wnt pathway, cell-cycle activation and β-amyloid; novel therapeutic strategies in Alzheimer's disease*? Trends Pharmacol. Sci. 24:233-238 (2003).

Chabry J. et al., *In vivo and in vitro neurotoxicity of the human prion protein (PrP) fragment P*1118-135 *independently of the PrP expression*, J. Neurosci. 23:462-469 (2003).

Chang, B-D. et al., *Effects of p21$^{Waf1/Cip/Sdi1}$ on cellular gene expression: implications for carcinogensis, senescence, and age-related diseases*, Proc. Nat. Acad. Sci, USA 97:4291-4296 (2000).

Ciulla et al., Sur. Ophthalm. 43:134-146 (1988).

Curcio et al., Inv. Ophthalm. Vis. Sci. 37:1236-1249 (1996).

Fakforovich et al., Nature 347:83-86 (1990).

Ge-Zhi et al., Trans. Am. Ophthalm. Soc. 94:411-430 (1996).

Gragoudas et al., Inv. Ophthalm. Vis. Sci. 38(4)S17 (1997).

Hock, C. et al., *Treatment with the selective muscarinic m*1 *agonist talsaclidine decreases cerebrospinal fluid levels of Aβ$_{42}$ in patients with Alzheimer's disease*, Amyloid: J. Prot. Fold. Disord. 10:1-6 (2003).

Husain et al., Ophthalm. 104(8):242-250 (1997).

Janus, C. et al., *Aβ peptide immunization reduces behavioural impairment and plaques in a model of Alzheimer's disease*, Nature 408:979-982 (2000).

Jen, L. S. et al., *Alzheimer's peptide kills cells of retina in vivo*, Nature 392:140-141 (1998).

Jensen L E and Whitehead A S, Biochem. J. 334:489-503 (1998).

Johan, K. et al., *Acceleration of amyloid protein A amyloidosis by amyloid-like synthetic fibrils*, Proc. Nat. Acad. Sci USA 95:2558-268 (1997).

Kane, M. D. et al., *Inhibitors of V-type ATPases, bafilomycin A*1 *and concanamycin A, protect against* β*-amyloid-mediated effects on* 3-(4,5-*dimethylthiazol*-2-*yl*)-2,5-*diphenyltetrazolium bromide* (*MTT*) *reduction*, J. Neurochem. 72:1939-1947 (1999).

Kindy, M. S et al., *Apolipoprotein serum amyloid A in Alzheimer's disease*, J. Alzheimer's Disease 1:155-167 (1999).

Koriyama, Y. et al., *Propentofylline protects* β*-amyloid protein-induced apoptosis in cultured rat hippocampal neurons* Eur. J. Pharmacol. 458:235-241 (2003).

Kumon, Y., Hosokawa, T., Suchiro, T., Ideda, Y., Sipe, J. D., and Hashimoto, K., *Acute-phase, but not constitutive serum amyloid A* (*SAA*) *is chemotactic for cultured human aortic smooth muscle cells*, Amyloid 9:237-241 (2002a).

Kumon, Y., Suchiro, T., Faulkes, D. J., Hosakawa, T., Ideda, Y., Woo, P., Sipe, J. D., and Hashimoto, K., *Transcriptional regulation of Serum Amyloid A*1 *gene expression in human aortic smooth muscle cells involves CCAAT/enhancer binding proteins* (*C/EBP*) *and is distinct from HepG*2 *cells*, Scand. J. Immunol. 56:504-511 (2002b).

Kumon, Y., Suchiro, T., Hashimoto, K., and Sipe, J. D., *Dexamethasone, but not IL*-1 *alone, upregulates acute-phase serum amyloid A gene expression and production by cultured human aortic smooth muscle cells*, Scand J. Immunol. 53:7-12 (2001).

Lambert, M. P. et al., *Diffusible, nonfibrillar ligands derived form Aβ$_{1-42}$ are potent central nervous system neurotoxins*, Proc. Nat. Acad. Sci. USA 95:6448-6453 (1998).

Lanz, T. A. et al., *The* γ*-secretase inhibitor N-*(*N*-(3,5-*difluorophenacetyl*)-*L-alanyl*]-*S-phenylglycine t-butyl ester reduces Aβ levels in vivo in plasma and cerebrospinal fluid*

in young (plaque-free) and aged (plaque-bearing) Tg2576 mice J. PHARMACOL EXPT. THER. 305:864-871 (2003).

LaVail et al., PROC. NAT'L ACAD. SCI. 89:11249-11253 (1992).

Liang, J. S., Sloane, J. A., Wells, J. M., Abraham, C. R., Fine, R. E., and Sipe, J. D., *Evidence for local production of acute phase response apolipoprotein serum amyloid A in Alzheimer's disease brain*, NEUROSCI. LETT. 225:73-76 (1997).

Lin et al., CURR. EYE RES. 13(7):513-522 (1994).

Liu, Y and Schubert, D., *Cytotoxic amyloid peptides inhibit cellular* 3-(4,5-*dimethylthiazol*-2-*yl*)-2,5-*diphenyltetrazolium bromide* (*MTT*) *reduction by enhancing MTT formazan exocytosis*, J. NEUROCHEM. 69:2285-2293 (1997).

Marks, N. and Berg, M. J., *APP processing enzymes (secretases) as therapeutic targets: insights from the use of transgenics (Tgs) and transfected cells*, NEUROCHEM. RES. 28:1049-1062 (2003).

Matsuoka, Y. et al., *Novel therapeutic approach for the treatment of Alzheimer's disease by peropheral administration of agents with an affinity for* β-*amyloid*, J. NEUROSCI. 23:29-33 (2003).

Miida T., Yamada, T., Yamadera, T., Ozaki, K., Inano, K., Okada, M., *Serum amyloid A protein generates pre-beta* 1 *high-density lipoprotein from alpha-migrating high-density lipoprotein*, BIOCHEM. 38(51):16958-16962 (1999).

Morgan, D et al., *Aβ peptide vaccination prevents memory loss in an animal model of Alzheimer's disease*, NATURE 408:982-985 (2000).

Naash et al., INV. OPHTHALM. VIS. SCI. 37:775-782 (1996).

Nakagami, Y and Oda, T., *Glutamate exacerbates amyloid* β1-42-*induced impairment of long-term potentiation in rat hippocampal slices*, JPN. J. PHARMACOL. 88:223-226 (2002a).

Nakagami, Y. et al., *A novel-sheet-breaker, RS*-0406, *reverses* β-*amyloid-induced cytotoxicity and impairment of long-term potentiation in vitro*, BR. J. PHARMACOL. 137:676-682 (2002b).

Noell et al., INVEST. OPHTHALM. VIS. SCI. 5:450-472 (1966).

O'Hara, R., Murphy, E. P., Whitehead, A. S., FitzGerald, O., and Bresnihan, B., *Acute-phase serum amyloid A production by rheumatoid arthritis synovial tissue*, ARTHRITIS RES. 2:142-144 (2000).

Pike, C. J. et al., *Neurodegeneration induced by* β-*amyloid-peptides in vitro: the role of peptide assembly state*, J. NEUROSCI. 13:1676-1687 (1993).

Schenk, D. et al., *Immunization with amyloid-*β*attenuates Alzheimer's-disease-like pathology in the PDAPP mouse*, NATURE 400:173-177 (1999).

Sickenberg et al., INV. OPTHALM. VIS. SCI. 38(4):S92 (1997).

Taylor et al., ARCH. OPHTHALM. 110:99-104 (1992).

Thomas et al., INV. OPHTHALM. VIS. SCI. 39(4):S242 (1998).

Thorn, C. F. and Whitehead, A. S., *Differential glucocorticoid enhancement of the cytokine-driven transcriptional activation of the human acute phase serum amyloid A genes, SAA*1 *and SAA*, J. IMMUNOL. 169:399-406 (2002).

Uhlar, C. M., and Whitehead, A. S., *Serum amyloid A, the major vertebrate acute-phase reactant*, EUR. J. BIOCHEM. 265:501-523 (1999).

Urieli-Shoval, S., Cohen, P., Eisenberg, S., and Matzner, Y., *Widespread expression of serum amyloid A in histologically normal human tissue. Predominant localization to the epithelium*, J. HISTOCHEM. CYTOCHEM. 46:1377-1384 (1998).

Walder et al., *Tanis: A link between type 2 diabetes and inflammation?* DIABETES 51:1859-1866 (2002).

Xia, W., *Relationship between presenilinase and* γ-*secretase*, DRUG NEWS PERSPECT. 16:69-73 (2003).

Yamada et al., *Serum amyloid A secretion from monocytic leukaemia cell line THP*-1 *and cultured human peropheral monocytes*, SCAND. J. IMMUNOL. 52:7-12 (2000).

Yamazaki et al., BIOCHEMICAL AND BIOPHYSICAL RES. COMM., 290:1114-1122 (2002).

Young, SUR. OPHTHALM. 32:252-269 (1988).

Zhang, L. et al., α-*Lipoic acid protects rat cortical neurons against cell death induced by amyloid and hydrogen peroxide through the Akt signaling pathway*, NEUROSCI. LETT. 312:125-128 (2001).

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Arg Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile
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Gly Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys
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Arg Gly Pro Gly Gly Ala Trp Ala Ala Glu Val Ile Ser Asn Ala Arg
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Glu Asn Ile Gln Arg Leu Thr Gly His Gly Ala Glu Asp Ser Leu Ala
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<400> SEQUENCE: 11

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20 25 30

Arg Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile
35 40 45

Gly Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys
50 55 60

Arg Gly Pro Gly Gly Ala Trp Ala Ala Glu Val Ile Ser Asn Ala Arg
65 70 75 80

Glu Asn Ile Gln Arg Leu Thr Gly Arg Gly Ala Glu Asp Ser Leu Ala
85 90 95

Asp Gln Ala Ala Asn Lys Trp Gly Arg Ser Gly Arg Asp Pro Asn His
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Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
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<212> TYPE: DNA
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Gln Lys Leu Ser Ala Arg Leu Arg Ala Leu Arg Gln Arg Gln Leu Asp
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Arg Ala Ala Ala Ala Val Glu Pro Asp Val Val Val Lys Arg Gln Glu
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Ala Leu Ala Ala Ala Arg Leu Lys Met Gln Glu Glu Leu Asn Ala Gln
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Val Glu Lys His Lys Glu Lys Leu Lys Gln Leu Glu Glu Glu Lys Arg
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Arg Gln Lys Ile Glu Met Trp Asp Ser Met Gln Glu Gly Lys Ser Tyr
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Lys Gly Asn Ala Lys Lys Pro Gln Glu Glu Asp Ser Pro Gly Pro Ser
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Thr Ser Ser Val Leu Lys Arg Lys Ser Asp Arg Lys Pro Leu Arg Gly
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Trp Asn Phe Asp Phe Val Thr Glu Thr Pro Leu Glu Gly Asp Phe Ala
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Trp Glu Arg Val Arg Gly Leu Gly Leu Pro Lys Leu Tyr Leu Pro Thr
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Thr Ser Met Thr Asp Phe Tyr His Ser Lys Arg Arg Leu Ile Phe Ser
145 150 155 160

Lys Arg Lys Pro

We claim:

1. A method for treating glaucoma, said method comprising topically administering to the eye of a patient in need thereof a therapeutically effective amount of a composition comprising a Tanis antagonist, wherein said Tanis antagonist is α-lipoic acid and wherein the concentration of α-lipoic acid in said composition is from 0.01% to 5% by weight.

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